

electrophoresis-free system, and attachment to solid support to confine the sample. With regard to Walt et al., it is asserted that the reference describes microbeads with attached nucleic acids randomly distributed on the surface of a fiber optic bundle so as to create a microbead array. It is further asserted that provided with Navot et al. and Walt et al., the skilled person would be motivated to use the microbead array of Walt et al. to detect the microbead reactions of Navot et al.

Briefly, the Navot et al. patent is directed to methods and kits of characterizing a GC rich region of a nucleic acid of interest, described in the patent as being genomic DNA or RNA derived from an individual for diagnostic purposes (see Abstract, column 10, lines 17-19). The Navot et al. patent does not disclose large scale sequence determination involving a plurality of target nucleic acids. Walt et al. is directed to compositions encompassing a substrate with a surface comprising discrete sites, and a population of microspheres distributed on the sites. The microspheres can include subpopulations of bioactive agent and corresponding optical signatures capable of identifying the corresponding bioactive agent (see Summary of the Invention).

To establish a *prima facie* case of obviousness, the Office must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385, 58 U.S.P.Q.2d 1286, 1293 (Fed. Cir. 2001); *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998); *Northern Telecom v. Datapoint Corp.*, 908 F.2d 931, 934, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, a hindsight analysis is not allowed. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); *In re Erlich*, 3 U.S.P.Q.2d 1011, 1016 (Bd. Pat. App. & Int. 1986). Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. See *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

For the reasons set forth below, the assertion that it would have been obvious for one skilled in the art to combine the cited references to arrive at Applicants' claimed invention is not accompanied by the required showing of where the cited references disclose the desirability of making the specific combination that is Applicants' presently claimed invention. Establishing that the prior art would have suggested the claimed method requires an underlying factual showing of a suggestion, teaching, or motivation to combine the prior art references and is an "essential evidentiary component of an obviousness holding." *Brown & Williamson Tobacco*, 229 F.3d at 1124-25 (quoting *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1351-52 (Fed.Cir.1998); see also *C.R. Bard* at 1351 (obviousness requires some suggestion, motivation, or teaching in the prior art where to select the components that the inventor selected and use them to make the new device); *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000) (there must be some motivation, suggestion or teaching in the prior art of the desirability of making the specific combination that was made by the applicant). The evidentiary showing must be clear and particular and broad conclusory statements about the teachings of the cited references, standing alone, are not "evidence." *Brown & Williamson Tobacco*, 229 F.3d at 1125 (quoting *In re Dembiczak*, 175 F.3d 994, 1000 (Fed.Cir.1999), abrogated on other grounds by *In re Gartside*, 203 F.3d 1305, 53 USPQ2d 1769 (Fed.Cir.2000)).

One purpose of the evidentiary requirement for showing a suggestion, motivation or teaching of the claimed combination is to prevent impermissible hindsight reconstruction of the claimed invention based on Applicant's own disclosure. *C.R. Bard*, 157 F.3d at 1352; *In re Dembiczak*, 175 F.3d 994, 999 ("[c]ombining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight"). In determining the validity of patented biopsy needle assembly over the sole assertion that it arose from obvious adaptations of a single prior art needle assembly to accommodate a new biopsy gun design, the court admonished against hindsight reconstruction when it stated:

The invention that was made, however, does not make itself obvious; that suggestion or teaching must come from the prior art. See, e.g., *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051-52, 5 USPQ2d 1434, 1438 (Fed.Cir.1988) (it is impermissible to reconstruct the claimed invention from

selected pieces of prior art absent some suggestion, teaching, or motivation in the prior art to do so); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed.Cir.1985) (it is insufficient to select from the prior art the separate components of the inventor's combination, using the blueprint supplied by the inventor); *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556, 225 USPQ 26, 31 (Fed.Cir.1985) (the prior art must suggest to one of ordinary skill in the art the desirability of the claimed combination).

The court went on to conclude that because no prior art provided a teaching, suggestion or motivation for the structure of the claimed needle assembly there was, as a matter of law, an absence of an essential evidentiary component for an obviousness finding. *C.R. Bard* at 1352.

Applicants respectfully maintain that the Office has not met the burden the law allocates to it with regard to establishing a *prima facie* case of obviousness.

The prior art references upon which the Office relies to support the present rejection do not give rise to the requisite motivation to combine their content. In particular, there has been no underlying factual showing that it would have been obvious to one of ordinary skill in the art to have modified the cited references by Navot et al. and Walt et al. to obtain the specific combination of elements of the claimed invention. The alleged motivation provided by Walt et al. is that synthesis of nucleic acids was separated from their placement on the array and random distribution of beads was inexpensive. However, the context of the statements relied upon by the Examiner is a comparison of methods for synthesizing random and spotted arrays and does not provide a motivation to combine the disclosures of Walt et al. and Navot et al.

This allows the synthesis of the bioactive agents (i.e. compounds such as nucleic acids and antibodies) to be separated from their placement on an array, i.e. the bioactive agents may be synthesized on the beads, and then the beads are randomly distributed on a patterned surface. Since the beads are first coded with an optical signature, this means that the array can later be "decoded", i.e. after the array is made, a correlation of the location of an individual site on the array with the bead or bioactive agent at that particular site can be made. This means that the beads may be randomly distributed on the array, a fast and inexpensive process **as compared to either the in situ synthesis or spotting techniques** of the prior art. Once the array is loaded

with the beads, the array can be decoded, or can be used, with full or partial decoding occurring after testing, as is more fully outlined below.

Walt et al., column 4, lines 44-59 (Emphasis added).

The Navot et al. patent is directed to the sequence determination of a particular GC-rich nucleic acid of interest derived from an individual to be diagnosed rather than a plurality of target nucleic acid sequences regardless of their base composition. A comparison of methods for synthesizing random and spotted arrays in the Walt et al. patent therefore would not have motivated the skilled artisan familiar with the Navot et al. patent to combine the two references. Without a motivation to combine, the present rejection is unsupported by the cited references and lacks the essential evidentiary component necessary to support an obviousness finding.

In view of the above arguments, Applicants respectfully request removal of the rejection of claims 1-4, 6-10, 12-17, and 22-27 as allegedly obvious under 35 U.S.C. § 103(a) over Navot et al., United States Patent No. 6,335,165, and Walt et al., United States Patent No. 6,327,410.

Applicants further respectfully traverse the rejection of claims 5 and 11, as allegedly obvious under 35 U.S.C. § 103(a) over Navot et al., *supra*, and Walt et al., *supra*, and further in view of Balch et al., United States Patent No. 6,083,763.

The patent by Balch et al. is cited as a further secondary reference merely for allegedly disclosing adapter probes, which are recited in claims 5 and 11. The Office Action, at page 4, cites a particular portion of the Balch patent that generally hails the manner in which adapter probes provide increased simplicity for users. As set forth above, a lack of motivation exists to combine Navot et al. and Walt et al. to arrive at Applicants' claimed invention. This deficit is not cured with regard to claims 5 and 11 by further citation of the Balch et al. patent. In addition, nothing in the Balch et al. reference would have provided a motivation to the skilled artisan to combine this reference with Navot et al., *supra*, and Walt et al., *supra*.

Given the initial lack of motivation described above with regard to combining Navot et al., *supra*, and Walt et al., *supra*, the statement that adapter probes provide a unique binding domain for each site on an array also does not provide motivation to combine Balch et al. with Navot et al., *supra*, and Walt et al., *supra*, to arrive at the claimed invention of claims 5 and 11. In view of the above arguments, Applicants respectfully request removal of the rejection of claims 5 and 11 as allegedly obvious under 35 U.S.C. § 103(a) over Navot et al., *supra*, and Walt et al., *supra*, and further in view of Balch et al., United States Patent No. 6,083,763.

Applicants further respectfully traverse the rejection of claims 18-21 and 28-30, as allegedly obvious under 35 U.S.C. § 103(a) over Navot et al., *supra*, and Walt et al., *supra*, and further in view of Nyren et al., WO 98/13523.

The international patent publication by Nyren et al. is cited at page 4, final paragraph, of the Office Action as a further secondary reference merely for allegedly disclosing kits encompassing a sequence primer, a polymerase, a detection enzyme means for identifying pyrophosphate release, dNTPs or ddNTPs. The Office Action asserts that both Navot et al. and Nyren et al. teach pyrosequencing and pyrosequencing kits with different sets of reaction components. The Office extrapolates this to be “strong motivation” to combine different reaction components into kits. It is respectfully submitted that the fact that two cited references each teach different sets of reaction components cannot be construed as strong motivation to make different combination as it could as plausibly be interpreted that one is an improvement of or teaches away from the other. Furthermore, as set forth above, a lack of motivation exists to combine Navot et al. and Walt et al. to arrive at Applicants’ claimed invention. This deficit is not cured with regard to claims 18-21 and 28-30 by further citation of the Nyren et al. patent publication. In addition, nothing in the Nyren et al. publication would have provided a motivation to the skilled artisan to combine this reference with Navot et al., *supra*, and Walt et al., *supra*.

With regard to Nyren et al., the Office Action, at page 9, first paragraph, further describes as necessary motivation that “kits were conventional in the field of molecular biology and provided the benefits of convenience and cost-effectiveness.” The Office is

respectfully reminded that the evidentiary showing must be clear and particular rather than based on broad conclusory statements about the teachings of the cited references. *See Brown & Williamson Tobacco*, 229 F.3d at 1125 (citations omitted). Rather than providing the necessary showing of a motivation to combine, the statement that kits were conventional, convenient and cost-effectiveness is conclusory and falls far short of the factual showing required to support an obviousness rejection. Given the initial lack of motivation described above with regard to combining Navot et al., *supra*, and Walt et al., *supra*, the statement that kits were conventional in the field of molecular biology and provided the benefits of convenience and cost-effectiveness does not provide motivation to combine Nyren et al. with Navot et al., *supra*, and Walt et al., *supra*, to arrive at the claimed invention of claims 18-21 and 28-30.

In view of the above arguments, Applicants respectfully request removal of the rejection of claims 18-21 and 28-30, as allegedly obvious under 35 U.S.C. § 103(a) over over Navot et al., *supra*, and Walt et al., *supra*, and further in view of Nyren et al., WO 98/13523.

### **CONCLUSION**

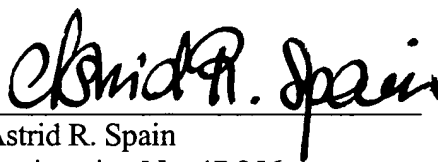
In light of the Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to contact the undersigned attorney with any questions related to this application.

Serial No.: 09/513,362

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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A handwritten signature in black ink, appearing to read "Astrid R. Spain", written over a horizontal line.

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